DIABETES MELLITUS AND ADDISON'S DISEASE

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DIABETES mellitus and Addison's disease in one patient is rare. Only in the past twelve years has it been well recognised in medical literature. The following case history is the sixty-ninth reported in the world and the third from Ireland. It is presented to produce a greater awareness to the likelihood of this combination of diseases, which modern therapy will make more common.

CASE HISTORY.

P. B., a female, now aged 43 years, has no family history of diabetes. A childhood bronchitis cleared at adolescence. From leaving school until marriage she worked as a shop assistant.

In 1947, when aged 28 years, during the sixth month of her third pregnancy, she became comatose and was diagnosed as having diabetes mellitus. The disease was of the juvenile type and difficult to control. During the six years following diagnosis she was in hospital on four occasions for stabilization. In October, 1953, she was discharged from hospital on a 2,200 calorie diet with a daily dose of twenty units of soluble insulin and thirty-two units of protamine zinc insulin.

For the next six years, from 1953 to 1959, she apparently remained well, failed to attend the diabetic clinic for supervision, and self-adjusted her dose of insulin according to how she felt.

She was admitted to the Belfast City Hospital on the 11th April, 1960, having had several attacks of nausea and general confusion during the previous two weeks. She had reduced her insulin dosage from fifty-two units to thirty-two units daily, but had produced no improvement in her condition. She was drowsy and dehydrated with a blood pressure of 110 mms. Hg. systolic and 70 mms. diastolic. Pigmentation of exposed skin areas was noted but not regarded as significant at this stage. Her urine gave a red-brown reaction with Benedict's Test, but contained no acetone.

A 1,500 calorie diet and forty units of Lente insulin daily produced a temporary clearing of the glycosuria. However, it became obvious over the following week that her diabetes was most unstable. Hypoglycæmic episodes followed bouts of glycosuria in a completely irregular manner. On the 21st April her general condition deteriorated with nausea, vomiting, and weakness. Clinically she appeared to be developing a hyperglycæmic coma. Although the blood sugars were moderately high, her urine was free from acetone. Electrolyte block on the 25th April showed marked dehydration with salt loss. Two days later her condition was critical. Although serum potassium levels were raised, electrocardiographic changes were in keeping with hypokalæmia. At this time the possibility of her dehydration not being diabetic was considered. Although the high potassium level and salt depletion of the blood could have been due to diabetic coma, it was thought her degree of drowsiness could not be produced without ketosis. As her coma deepened it was decided to give her corticoid therapy as there was the possibility of adrenal failure. An initial dose of 100 mgs. of hydrocortisone was given intravenously followed by a daily intramuscular

injection of 5 mgs. of D.O.C.A. Cortisone was administered orally in six hourly doses of 50 mgs., later being reduced to 25 mgs. three times daily. Over the next few days there was an immediate improvement and she continued to keep well.

In spite of her response to corticoids, there was still much controversy as to the cause of her illness. One view was that she had had a diabetic coma with osmotic diuresis, loss of sodium chloride and peripheral circulatory failure; the other that the patient had had adrenal failure. Corticoid treatment was gradually discontinued and the patient was discharged on the 17th May for observation on a trial of 1,500 calorie diet with thirty units of soluble and thirty-six units of protamine zinc insulin daily.

On the 28th May she was re-admitted in a severe hypoglycæmic coma. This was controlled by routine treatment. Adrenal failure was again reconsidered. Straight X-ray abdomen showed no calcification. X-ray skull was normal. Levels of 17 keto-steroids in twenty-four hour samples of urine were 1.9 mgs. and 2.3 mgs. Seventeen ketogenic steroid level was 2.4 mgs. in twenty-four hour urine. She again developed peripheral circulatory failure on the 15th June. It was not felt to be justifiable to withhold therapy to prove the diagnosis by an A.C.T.H. stimulation test. She was again commenced on corticoid therapy, responded, and was finally controlled by cortisone 25 mgs. orally three times per day and fluorohydrocortisone 0.1 mg. orally daily. Her diabetes was satisfactorily stabilized on a daily dose of ten units of soluble insulin and twenty-four units of protamine zinc insulin.

She went home on the 4th July, 1960. Since then the pigmentation has disappeared, except for patches on her neck and knees, and her blood pressure has been maintained at 140 mms. Hg. systolic and 90 mms. Hg. diastolic. Blood sugar levels are controlled within reasonable limits by visits to the clinic at two-monthly intervals. She has gained a stone in weight and has been able to live an active full life.

Discussion.

Modern therapy has improved the prognosis in both diabetes mellitus and Addison's disease. The increased life expectancy has rendered the opportunity of their association more likely. A growing awareness of this association may be a factor in the increased frequency of reports in recent years.

In this patient the diagnosis of Addison's disease was accepted on the following findings:—

(1) Generalised body pigmentation, more marked on the neck and dorsum of hands and forearms. A small patch of buccal pigmentation. The pigmentation disappeared on corticoid therapy.

(2) Hypotension. The mean of blood pressure readings recorded twice daily following first admission was 100 mms. Hg. systolic and 60 mms. Hg. diastolic.

(3) Two acute hypotensive episodes of twelve hours' duration associated with peripheral circulatory failure. These responded to intravenous hydrocortisone.

(4) The recent onset of an unusual sensitivity to insulin.

(5) Reduced levels of urinary excretion of 17 keto-steroids and 17 ketogenic steroids.

(6) Serum electrolyte levels (see figure).

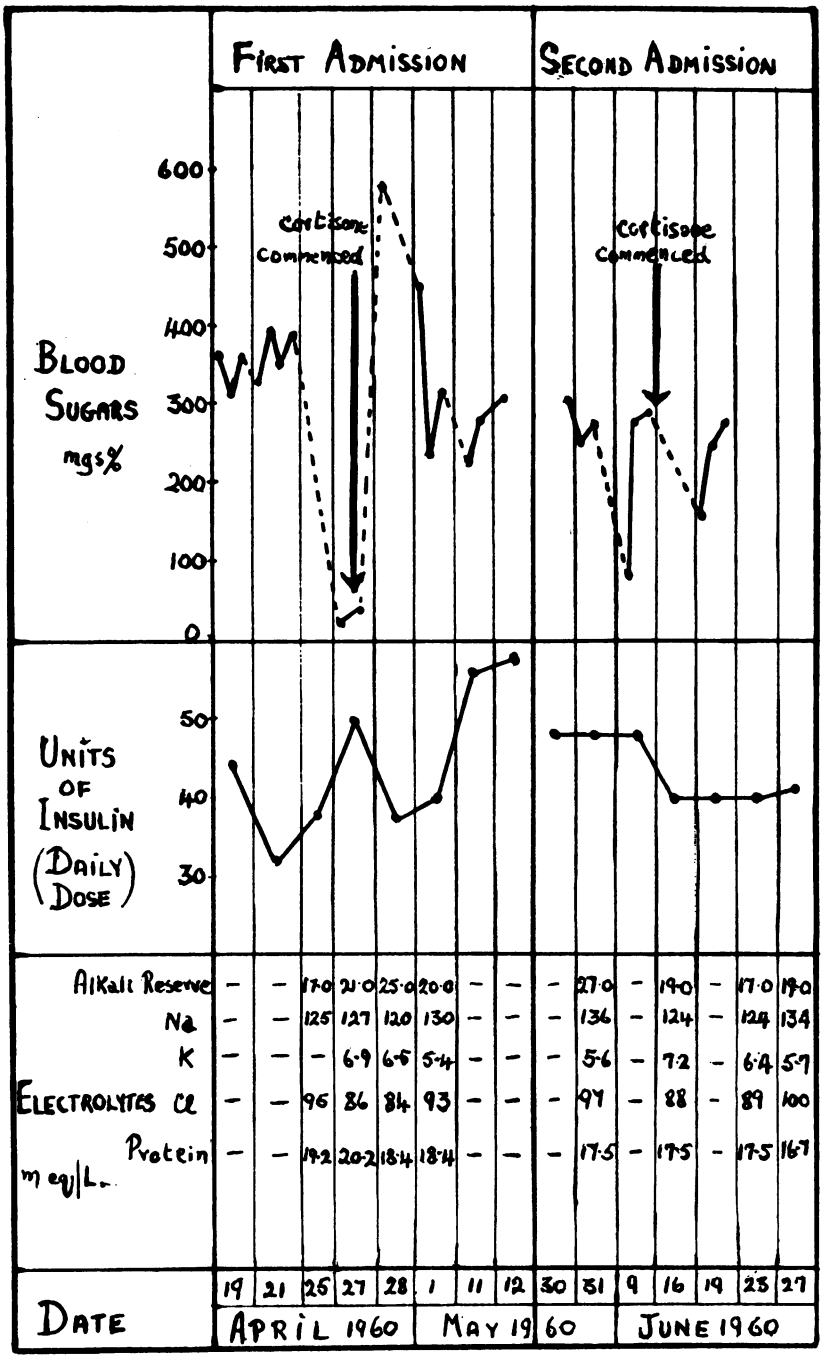

Figure. Insulin Dosage, Blood Sugar, and Serum Electrolyte Results.

During both attacks of circulatory failure the patient had salt depletion and hyperkalæmia. This electrolyte imbalance may present in either hyperglycæmia or Addisonian crisis.

In the former the increased concentration of glucose produces an osmotic diuresis which inhibits the reabsorption of sodium. The fall in blood and extracellular volume causes a withdrawal of fluid from cells carrying potassium into the blood. Lack of insulin also inhibits glucose utilisation and prevents movement of serum potassium into the cell. A high blood potassium level results but may co-exist with a cellular deficiency.

In the latter the deficiency of adrenal cortical hormones causes a derangement of the mechanisms concerned with the reabsorption of sodium, potassium, and chloride by the renal tubular epithelium. There is a decreased reabsorption of sodium and chloride with an increased reabsorption of potassium.

The reduced glomerular filtrate rate in peripheral circulatory failure may produce little effect on potassium levels. Filtered potassium does not constitute any large part of the potassium ultimately excreted, potassium in urine being excreted by a process of tubular secretion.

That the electrolyte imbalance in the present patient was due to adrenal insufficiency was based on the absence of acetonuria. Blood sugar levels alone were not elevated enough to produce such a degree of dehydration.

It is difficult to give an explanation for the patient's raised serum potassium level coinciding with hypokalæmic electrocardiographic changes. The various E.C.G. abnormalities of hypokalæmia, e.g., ST depression with prolonged QT and prominent U waves have all been described in association with low serum potassium levels. Little is known of the influence of intracellular potassium.

Diabetes mellitus and Addison's disease exert opposite effects on carbohydrate metabolism. The absence of hydrocortisone in Addison's disease decreases glucose formation from protein precursors and increases peripheral utilisation of glucose (Conn and Fajans, 1956). In diabetes glycogen formation in liver and muscles, carbohydrate utilisation and dissimulation by the tissues, and the conversion of glucose to long chain fatty acids are all decreased (Samson Wright, 1961). Thus in diabetes mellitus complicated by Addison's disease there is an apparent improvement in carbohydrate metabolism, a tendency to hypoglycæmia and a reduction in insulin requirement. This patient finally required only thirty-four units of insulin daily, in spite of taking cortisone, compared with fifty-two units daily which previously had controlled her satisfactorily for some years. The well-controlled Addison's disease developing diabetes has an exacerbation of adrenal insufficiency. Gittler, Fajans, and Conn (1959) suggest this is due to the osmotic diuresis provoked by the glycosuria causing a secondary renal loss of salt and water.

Beaven, Nelson, Renold, and Thorn (1959) reviewed sixty-three reported cases of Addison's disease and diabetes mellitus dividing them, according to their onset, into three groups. Twenty-one had an initial diagnosis of Addison's disease later complicated by diabetes, thirty-seven developed the diabetes primarily, and five had a simultaneous onset of both conditions. The present reported case

history is typical of the second group in which all but eight required a reduction in insulin dosage with the onset of Addison's disease. Twenty-one of the thirty-seven had insulin hypoglycæmia as one of the presenting symptoms.

Simpson (1949) suggests the co-existence of adrenal and islet cell atrophy may be due to a common infective lesion. If this is so, the infecting agent is unlikely to be the tubercle bacillus. Only in a very small minority of the published cases has a tuberculous ætiology been suggested. During recent years, when the frequency of reports of this dual pathology has increased, tuberculosis in diabetes has shown a steady decrease. The present patient had a normal chest radiograph and no evidence of adrenal calcification on straight X-ray of abdomen, although her husband had had tuberculosis.

Many of the reported cases of Addison's disease and diabetes have been diagnosed only at post-mortem. The onset of Addison's disease should be suspected when there is an improvement in the diabetic syndrome with reduced insulin requirements and hypoglycæmic aattacks. This must be differentiated from the following conditions which have also been reported as producing amelioration in diabetes—hypopituitarism (Martin and Pond, 1954), hypothyroidism (Rupp, George, and Paschkis, 1955), Kimmelstiel-Wilson's syndrome (Zubrod, Eversole, and Dang, 1951), insulinogenic tumour of the pancreatic islets (Gittler, Zucker, Eisenger, and Stoller, 1958), hæmochromatosis (Simpson, 1949), and liver cirrhosis (Bordley, 1930).

In treatment, earlier reports have advised caution both in the use of steroids and insulin, in the former due to the danger of producing uncontrollable hyperglycæmia and ketosis, and in the latter due to the insulin sensitivity of the Addisonian patient. Leahy (1959) advises the immediate use of hydrocortisone in amounts large enough to control the Addisonian state or crisis followed by an early introduction of insulin as soon as the hyperglycæmic effect of the hydrocortisone becomes apparent. In maintenance therapy fluorohydrocortisone is now standard treatment, the advantage being its reduced glucogenic effect relative to cortisone.

With the present advances in therapy it is difficult to give a prognosis in these patients. Faber and Gronboek, surveying fifty-six cases previous to 1956, give the average duration of life after diagnosis as five years. Simpson (1949) states death does not occur from diabetic coma but from adrenal insufficiency or possibly hypoglycæmic coma. However, in one of two cases reported by Markovitz (1954) diabetic acidosis occurred three times in relation to exacerbations of otitis media. He remarks on the interesting fact that this patient was on a fixed dose of cortisone and questions the accepted view that the metabolic upset with stress in the uncomplicated diabetic is due to increased secretion of adrenocortical hormones.

SUMMARY.

A further case of Addison's disease complicating diabetes mellitus has been described. This dual pathology, although being more frequently recognised, is still rare. The condition has been briefly reviewed in relation to diagnosis, treatment, and prognosis.

ACKNOWLEDGMENTS.

This case was under the care of Dr. Alan P. Grant, to whom I am greatly indebted not only for permission to publish, but also for his helpful and stimulating criticism.

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REVIEW

CLAYTON'S ELECTROTHERAPY AND ACTINOTHERAPY. By Pauline M. Scott, M.C.S.P., T.E.T., T.M.M.G. (Pp. 384; figs. 200. 30s.) London: Baillière, Tindall & Cox, 1962.

THIS fourth edition in fourteen years confirms the value and demand of this well-recognised standard text book for physiotherapy students during their training for the M.C.S.P. qualification. It is also of great value in reading for the Diploma in Physical Medicine. The general layout is excellent and makes for easy reference, pleasant reading, and is very adequate in the identification of the various modalities of low and high frequencies currents, ultra-violet radiation, ultra-sonic therapy; with application, necessary precautions, and contra-indication clearly defined.

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